# Reforming Clinical Trials in Drug Development: Impact of Targeted Therapies

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# IT'S NOT JUST THE TRIAL, IT'S THE DEVELOPMENT PROGRAM

# Success Depends Less on Novel Trial Design than on the Knowledge that Underpins the Program

- Understanding natural history—what will happen to people in the trial, and when?
- If you are using novel clinical endpoints, or standard endpoints in a new disease, how will they perform?
- What about PROs?
- Power calculations are not enough, you should model and simulate based on what you know, to see if design is feasible

# Common Problems in Rare Diseases and Disease Subsets

- Natural history of the disease or disease subset not clear
  - For disease subset, includes prognosis compared to overall disease
- Biomarker measurements, their discriminatory performance, cutoffs, etc not well worked out
- Outcome measures for disease have never, or rarely, been tested
- Overall development plan not a whole
- Murphy's law operates

# So What's a Developer to Do?

- Develop as comprehensive an idea of the natural history as possible
  - Involve patients
  - Do not simply consult experts on their experience
- Qualify all proposed biomarkers and outcome measures as thoroughly as possible, *before* starting to rely upon them
- Conduct a seamless, adaptive development program

# Natural History of Disease: Critical to Planning a Development Program

- Burden of disease
  - What are the symptoms?
  - What would patients most like to have relieved?
  - Are there instruments to measure these?
  - Tradeoffs: how much risk is acceptable for benefits?
- Rate of progression of symptoms
  - Over what time period does measurable change occur?
  - What symptoms progress faster and is this true for everyone?
  - Don’t just rely on experts, they are usually wrong, due to sampling bias

# Natural History

- Disease heterogeneity
  - Often, rare diseases are heterogeneous in their expression; rare subsets may or may not be
  - Introduces more variability, which is the bane of finding signal within noise
  - With highly variable disease, self controlled trials may be best
- Many natural history studies are done by academia through registries, etc. May lack documentation, may not be representative sample

# Gathering Reliable Natural History Data

- Patient advocacy groups increasingly involved
- NORD, Genetic Alliance, others (FDA Orphan product grant) supporting efforts
- Usually any of these, or academic registries, will need bolstering to provide information adequate to intelligently design a development plan for an intervention
- Start well before product slated to enter clinical development—you need these data as early as possible

# Conundrums with Existing Natural History Data

- Biomarkers rarely defined and measured rigorously
- Clinical outcomes rarely well described in uniform fashion
- Longitudinal followup may be limited
- Various forms of bias may be present in selection of patients who were followed—or patients with particular characteristics required for targeted therapy may not be identified

# Biomarker Issues

- Development program may be centered around a predictive (of patient response) or prognostic (for patient selection), or pharmacodynamic (for assessing activity) biomarker
- The crucial biomarkers may not be reproducible, precise, accurate, or informative. Their operating characteristics may not be known and how to designate a “positive” response (e.g. a threshold or cutoff) may be unexplored

# Biomarker Issues

- Relying on the performance of such a biomarker as the basis for a clinical development program is folly, in my view
- However, some pragmatic compromises must be made
- Biomarkers critical to a development program should be explored, *in humans,* as thoroughly as possible, prior to initiating human studies
- If the biomarker is to be used for a critical purpose, for example patient selection or pharmacodynamic readout, remaining uncertainty should be addressed as part of the development program, potentially using an adaptive design.

# Trial Designs in the New Era

# Development Program Clusters Based on Clinical Situation

- Rare, life-threatening disease with no good treatment, targeted therapy reasonably expected (perhaps from early data) to have large treatment effect (e.g., breakthrough drug). Similarly for biomarker-identified subset of life-threatening disease with no good treatment. (often oncology)
- In this situation may see
  - "Extended Phase 1 Cohort"  approval
  - Endpoints (cancer): response rate, PFS

# Very Rare Diseases: Examples of FDA Approvals

- Lumizyme for Pompe Disease:  survival data from an international registry of infantile-onset disease
- Carbaglu:  Plasma level ammonia reductions in a case series
- Cholbam for bile acid synthesis disorders: data on growth, survival and reduction in abnormal cholestatic markers  in a case series
- Glucarpidase for MTX toxicity: data on approx. 20 patients from NIH treatment protocol

# What did These have in Common?

- Highly plausible mechanistic hypothesis
- Natural history data on untreated patients
- Highly plausible biomarkers; most could be measured in a standard manner
- Serious unmet medical need
- Relatively large treatment effect

# Development Programs for Ultra-Rare Diseases

- Performing standard clinical trial may be very difficult
- N-of-1 studies looking at disease trajectory (e.g., slopes of various declines pre and post rx) may be feasible. Start observational part early.
- Data from natural history may be helpful if treatment results in a convincing departure and disease not too heterogeneous
- Oncology: “basket” trials with biomarker defined targets across histologic diagnoses; NCI “MATCH” trial
- Emergencies: NIAID Ebola trial with adaptive design and Bayesian analysis

# Rare, Serious Disease, Size of Treatment Effect Unknown

- You cannot plan for a huge treatment effect to wipe out all the other problems
- “Randomize the first patient” (maybe not the very first, but randomization is the key to efficiently finding if there is a treatment effect)
- Dose-finding can be randomized, adaptive, include placebo arm
- If you expect the need for longer duration of therapy needed to see effect, build in interim analyses, you need not lose that much alpha

# Clinical Situation: Serious, Rare or Uncommon Disease with Existing SOC

Opportunity to randomize early without using placebo

- Will need to do comparative trial unless new therapy is of obvious "breakthrough" stature and SOC is not very good
- Master protocols trying to address:
  - LungMapp: NSCLC randomize all comers at 2nd line to a biomarker-defined therapy vs SOC. Screening trial to ID biomarker-drug pairs
  - I-SPY 2: Poorer Px breast cancer, screen biomarker-drug pairs in neoadjuvant setting, "graduate" to definitive adjuvant trial vs. SOC

# Clinical Situation: Common Disease with SOC

- Expectation that new therapy will be at least as useful as existing therapy
  - Perhaps for intolerant patients
  - Perhaps better safety profile

  Usually looking a 2 NI trials for efficacy

  If intolerant patients, should document this before enrollment, if SOC has “failed” should document how

# Biomarker Endpoints: Accelerated Approval

- If planning program: need to reach agreement that biomarker is “reasonably likely to predict clinical benefit”
- Then generate “substantial evidence” on effect on biomarker
- Randomization usually best design in this situation, given that biomarker effects are generally less persuasive than clinical effects

# Use of Predictive Biomarker to Select Patients: Does it Discriminate?

- Current experience shows that target status often correlates with *magnitude* of treatment effect, but there is no cutoff (for continuous biomarker)
- If you want to have a large treatment effect, may utilize cutoff
- If you want to include all responding patients, might incorporate a randomized design stratified by biomarker status. You could model how to adaptively manage the cutoffs based on the incoming data to get to a sweet spot of response and biomarker positivity

# Use of Real World Evidence (RWE)

- There are no hard and fast rules about how evidence is generated, with the exception of informed consent and patient privacy
- Settings can vary along a spectrum from the standard clinical trial setup to a pragmatic trial run in the healthcare system(s).
- There are trade-offs among data reliability, pragmatism, control of errors, safety, and other factors
- Clearly you don’t want to run a first-in-human trial in the real world setting, for example

# FDA is Evaluating Use of RWE

- Clearly, we have approved drugs for rare diseases based on data from registry-like case series
- We are exploring how randomization would work in registry or healthcare settings
- We are collaborating with groups working to improve the validity of key data elements collected in the process of health care, eg her
- We have spoken to many groups that are assembling oncology care data in various ways and hope to provide valid platforms for investigations

# Use of RWE

- NIH “Collaboratory” carrying on trials in real world setting—up front investment with providers but with very low per-patient costs
- Neonatal consortium:  neonatologists organizing clinical trial network for NICUs—patients already “fully wired”
- Conversations on carrying on randomized trials in more-organized health care settings—feasible, but more questions remain

# Summary

- Trial designs, no matter how novel, will only be as good as the knowledge that underlies them
- No matter how advanced the design, you may be in trouble if you have too many variables in play in your very expensive clinical development program:
  - Variability in disease expression or progression
  - Lack of specificity of dx, px, or predictive biomarkers
  - Unknown or poor performance of COA's
  - PROs that don't reflect the patient's view of burden of disease

  Advanced design won't cure the above unless you actually build exploration of them into your trial

# Conclusion

- Targeted, personalized, or precision medicine approaches can deliver large treatment effects, making development easier
- Adequately-performing diagnostic, prognostic and predictive biomarkers are key to enrolling the right patient population, and this is not as straightforward as was initially thought
- Understanding the performance of COAs is critical to picking the right endpoints
- All the above much more crucial, with a smaller treatment effect